

Express Mail Label No. EV 336 040 092 US

Attorney Docket No. 59150-8010

In the Specification

On page 9, please replace the paragraph starting on line 30 with the following:

Figures 8A-8C [[is an]]are electron micrographs of an HVJ envelop vector using negative staining, showing (1) untreated HVJ (Fig. 8A); (2) HVJ containing no DNA, which was subjected to an octylglucoside treatment (Fig. 8B); and (3) HVJ containing DNA, which was subjected to an octylglucoside (Fig. 8C).

On page 10, please replace the paragraph starting on line 12 with the following:

Figures 10A-1 to 10A-3 and 10B-1 to 10B-3 are graphs representing gene transfer efficiency represented in terms of luciferase activity levels which were taken at the respective protamine sulfate (PS) concentrations and the respective transfection times, as shown in the figures.

On page 10, please replace the paragraph starting on line 18 with the following:

Figures 11A-1 to 11A-2 and 11B are graphs representing gene transfer activity levels which were taken at the respective DNA amounts (amounts used in the experiment), and the respective storage temperatures, as shown in the figures.

On page 12, please replace the paragraph starting on line 7 with the following:

Figures 16D-1 to 16D-3 shows the results of administering HVJ envelope vectors containing pEGFP-1 of 10,000 HAU to DS rats (male, body weight: 300 to 400 g) via the cisterna magna or via the carotid artery. Three to four days after the administration, the rats were sacrificed, and live sections were prepared, which were subjected to observation under fluorescence microscopy.

On page 12, please replace the paragraph starting on line 15 with the following:

[[①]]Figure 16D-1: administration via the cisterna magna

On page 12, please replace the paragraph starting on line 21 with the following:

[[②,③]]Figures 16D-2 and 16D-3: administration via the carotid artery

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On page 13, please replace the paragraph starting on line 6 with the following:

Figures 17A-1 to 17A-2 and 17B-1 to 17B-2 show results of cell fluorescence observed under fluorescence microscopy on the next day of introduction of oligonucleotides into cells. About 10% oligonucleotide introduction efficiency was obtained after 10 minutes of incubation (Figure 17B-1 and 17B-2), whereas the oligonucleotides were introduced into 80% or more of the cells after 60 minutes of incubation (Figure 17A-1 and 17A-2).

On page 36, please replace the paragraph starting on line 10 with the following:

The results are shown in Figures 8A-8C. A majority of the HVJ envelope vectors had substantially the same outer configuration as that of the HVJ virus observed in the past itself. As compared with the HVJ envelope vector in which DNA was not encapsulated, a structure having a high electron density was observed in the HVJ envelope vector in which DNA was employed. On the other hand, the unencapsulated HVJ envelope vectors had a high internal transmittance, and it was inferred that the virus genome had been destroyed or lost.

On page 39, please replace the paragraph starting on line 13 with the following:

The results are shown in Figures 9A-9C.

On page 40, please replace the paragraph starting on line 11 with the following:

The results are shown in Figures 11A-1 to 11A-2 and 11B.

On page 43, please replace the paragraph starting on line 31 with the following:

(13.3: rat brain)

An HVJ envelope vector containing pEGFP-1 (i.e., a vector where a green fluorescence protein gene (about 037kb) of jellyfish is incorporated into an expression vector having a cytomegalovirus promoter; available from Clontech, Palo Alto, CA) was prepared by a method similar to the aforementioned method for preparing an HVJ

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envelope vector containing pcLuci. Thirty microliters of the vector (equivalent to 1000 HAU, 1/10 of the preparation) was injected into either the carotid artery or the intrathecal space via the cisterna magna of SD rats (Sprague-Dawley rats). Three to four days after the gene transfer, the rats were sacrificed, and brain sections were prepared without fixation. Fluorescence was observed under fluorescence microscopy. As indicated by the results shown in Figures 16D-1 to 16D-3, intracerebral expression of green fluorescence protein (GFP) was observed with both injection into the carotid artery and injection into the intrathecal space via the cisterna magna. On the other hand, intracerebral GFP expression was not observed when a similar gene transfer was performed via the rat carotid artery by using HVJ-AVE liposome.

On page 46, please replace the paragraph starting on line 4 with the following:

Twenty-mer oligonucleotides (5'-CCTTgAAGGGATTCCCTCC-3') (SEQ ID NO: 1) (194 μ g/92 μ l of BSS), which were labeled at the 5' position with FITC, were mixed with a precipitate of HVJ of 10,000 HAU (which had been inactivated with 198 mJ/cm² of UV light). Triton X-100 (final concentrations 0.24%) was added, and the mixture was subjected to a treatment on ice for 1 minute. One milliliter of BSS was added, and the mixture was centrifuged (15,000 rpm, 15 minutes, 4 °C.). To the precipitate, 100 μ l of PBS was added, and the mixture was stored at -20 °C. One month later, the mixture was thawed, and 10 μ l thereof was mixed with 5 μ g of protamine sulfate, and incubated (10 minutes, 60 minutes) with 5,000,000 BHK-21 cells (in a 0.5 ml of medium). On the next day of the introduction, the cell fluorescence was observed under fluorescence microscopy. As a result, about 10% oligonucleotide introduction efficiency was obtained after 10 minutes as shown in Figure 17B-1 and 17B-2, whereas the oligonucleotides were introduced into 80% or more of the cells after 60 minutes as shown in Figure 17A-1 and 17A-2.

On page 46, please replace the paragraph starting on line 32 with the following:

Double-strand nucleic acids having a Stat6 DNA binding sequence (5'-GATCAAGACCTTTCCCAAGAATCTAT-3') (SEQ ID NO: 2) and 3'-

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CATGTTCTGGAAAAGGGTTCTTAGATA-5' (SEQ ID NO: 3), (Wang, L. H. et al.: Blood 95, 1249 to 1257, 2000)) (250 µg/300 µl of BSS) were mixed with a precipitate of HVJ of 30,000 HAU (which had been inactivated with 99 mJ/cm² of UV light).

On page 48, please replace the paragraph starting on line 6 with the following:
The cell lines used (in particular CCRF-CEM and NALM-6) show a very low introduction efficiency in the case where HVJ-liposomes or existing liposome reagents (Lipofectamine, Lipofectin of Gibco BRL, etc.) are used. However, as shown in Figures 18A and 18B to 18C, a highly efficient gene transfer to these cell lines was observed. The samples were run in duplicate and each bar at each protamine sulfate concentration and centrifugation rpm corresponds to the sample tested in duplicate.

In the specification after page 53, please insert the Sequence Listing on page 1, enclosed herewith.